JPW

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

WRITTEN OPINION

(PCT Rule 66)

To: JOHN P. WHITE
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RECEIVED
COOPER & DUNHAM
JUN 25 2001

Reply to Written Opinion: 8/22/01

Date of Mailing *(day/month/year)*	22 JUN 2001
Applicant's or agent's file reference: 59167-A-PCT	REPLY DUE within TWO months from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/22060	11 AUGUST 2000	13 AUGUST 1999 ✓

International Patent Classification (IPC) or both national classification and IPC
Please See Supplemental Sheet.

Applicant
THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK

1. This written opinion is the first (first, etc.) drawn by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

   - I [X] Basis of the opinion
   - II [ ] Priority
   - III [ ] Non-establishment of opinion with regard to novelty, inventive step or industrial applicability
   - IV [ ] Lack of unity of invention
   - V [X] Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI [ ] Certain documents cited
   - VII [ ] Certain defects in the international application
   - VIII [X] Certain observations on the international application

3. The applicant is hereby invited to reply to this opinion.

   When? See the time limit indicated above. ~~The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).~~

   How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

   Also For an additional opportunity to submit amendments, see Rule 66.4.
   For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 *bis*.
   For an informal communication with the examiner, see Rule 66.6.

   If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 13 NOVEMBER 2001.

Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer SHIN-LIN CHEN Telephone No. (703) 308-0196

Form PCT/IPEA/408 (cover sheet) (July 1998) ★

[redacted] WRITTEN OPINION

[redacted] application No.
PCT/US00/22060

I. Basis of the opinion

1. With regard to the elements of the international application:*

[X] the international application as originally filed

[X] the description:
pages 1-70, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of

[X] the claims:
pages 71-75, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of

[X] the drawings:
pages 1-35, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of

[X] the sequence listing part of the description:
pages 1-5, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language ___ which is:

[ ] the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

[ ] the language of publication of the international application (under Rule 48.3(b)).

[ ] the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

[X] contained in the international application in printed form.

[X] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readable form.

[ ] The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] The statement that the information recorded in computer readable form is identical to the writen sequence listing has been furnished.

4. [X] The amendments have resulted in the cancellation of:

[X] the description, pages NONE

[X] the claims, Nos. NONE

[X] the drawings, sheets/~~fig~~ NONE

5. [ ] This opinion has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

** Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*

WRITTEN OPINION

International application No.
PCT/US00/22060

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. statement

Novelty (N)	Claims	1-26	YES
	Claims	NONE	NO
Inventive Step (IS)	Claims	4, 5, 15, 16, 18	YES
	Claims	1-3, 6-14, 17, 19-26	NO
Industrial Applicability (IA)	Claims	1-26	YES
	Claims	NONE	NO

2. citations and explanations

Claims 1-3 and 6-14 lack an inventive step under PCT Article 33(3) as being obvious over Gayle et al., 1998 in view of GenCore Accession No. WO4334, 1996.

Claims 1-3 and 6-14 are directed to a method for treating or preventing stroke in a subject comprising administering a CD39 polypeptide, such as soluble CD39 (SEQ ID No. 2), or an active fragment comprising 1-50 amino acids or 20-80 amino acids of SEQ ID No. 1, that inhibits ADP-mediated platelet aggregation. The claims further are drawn to administering the CD39 polypeptide or its active fragment prior to, at the onset of, or after stroke at various dosages, such as 1-20 mg/kg or 4-8 mg/kg of the subject's body weight.

Gayle teaches a soluble form of CD39, which is an ecto-enzyme with ADPase and ATPase activities, blocks ADP-induced platelet aggregation in vitro, and inhibits collagen-induced platelet reactivity. Gayle also suggests the soluble form of CD39 with full ADPase activity might constitute a novel approach to prevention and/or treatment of thromboembolic disease including stroke (e.g. abstract, introduction, p. 1857). Gayle does not teach the presence of CD39 having the sequence of SEQ ID No. 1 or 2.

GenCore Accession No. WO4334 presents a polypeptide sequence that is 100% identical to SEQ ID No. 1 or 2, and said polypeptide sequence is a human lymphoid cell activation antigen CD39 and could be used in reduction of platelet aggregation and of thrombogenicity.

It would have been obvious for one of ordinary skill at the time of the invention to use the CD39 polypeptide as taught by GenCore Accession No. WO4334 to prevention and/or treatment of thromboembolic disease including stroke as taught by Gayle because it was known that CD39, which is an ecto-enzyme with ADPase and ATPase activities, blocks ADP-induced platelet aggregation in vitro, and inhibits collagen-induced platelet reactivity. It would have been obvious for one of ordinary skill to administer a compound prior to, at the onset of, or after stroke at various dosages in the method taught by Gayle because they are routine optimization of result-effective variables and is obvious to a person of ordinary skill.

(Continued on Supplemental Sheet.)

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: Boxes I - VIII

TIME LIMIT:

The time limit set for response to a Written Opinion may not be extended. 37 CFR 1.484(d). Any response received after the expiration of the time limit set in the Written Opinion will not be considered in preparing the International Preliminary Examination Report.

CLASSIFICATION:

The International Patent Classification (IPC) and/or the National classification are as listed below:
IPC(7): A01K 67/00, 67/033; A61K 38/43; C07K 1/00; C12N 9/00 and US Cl.: 424/94.1; 435/183; 514/2; 530/348.25; 800/8, 9, 13, 18

V. 2. REASONED STATEMENTS - CITATIONS AND EXPLANATIONS (Continued):

Claims 17 and 19-26 lack an inventive step under PCT Article 33(3) as being obvious over Guth et al., 1997 in view of Gayle et al., 1998.

Claims 17 and 19-26 are directed to a method for determining whether a compound inhibits platelet aggregation by increasing ADP catabolism so as to treat or prevent thrombotic or ischemic disorders in a subject by using an animal model and measuring platelet deposition, fibrin deposition, bleeding time, or infarction volume. The claims further are drawn to administering a compound prior to, at the onset of, or after stroke and a pharmaceutical composition comprising the compound identified, such as a CD39 polypeptide or an active fragment thereof.

Guth teaches using a BIBU52, a nonpeptide molecule, to block GPIIb/IIIa receptor so as to inhibit platelet aggregation both in vitro and in vivo animal models including guinea pig, pigs, and marmoset monkeys. Guth induces thrombus by damaging aorta with a hemostatic clamp and measuring the rate of thrombus formation, bleeding time, or mean blood-flow velocity with or without the administration of the compound BIBU52. Guth does not teach using CD39 polypeptide to inhibit platelet aggregation.

Gayle teaches a soluble form of CD39, which is an ecto-enzyme with ADPase and ATPase activities, blocks ADP-induced platelet aggregation in vitro, and inhibits collagen-induced platelet reactivity. Gayle also suggests the soluble form of CD39 with full ADPase activity might constitute a novel approach to prevention and/or treatment of thromboembolic disease including stroke (e.g. abstract, introduction, p. 1857).

It would have been obvious for one of ordinary skill at the time of the invention to use the CD39 polypeptide taught by Gayle to test its ability in inhibiting platelet aggregation in in vivo animal models as taught by Guth and be able to identify CD39 polypeptide could inhibit platelet aggregation by increasing ADP catabolism so as to treat or prevent thrombotic or ischemic disorders in a subject because of the teaching of Gayle. It would have been obvious for one of ordinary skill to administer a compound prior to, at the onset of, or after stroke in the method taught by Guth because they are routine optimization of result-effective variables and is obvious to a person of ordinary skill.

Claims 4, 5, 15, 16 and 18 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest having IL-2 as CD39 leader sequence, using saline, liposome, or anti-stroke agent as a carrier, or using a CD39-deficient mouse as an animal model.

---------- NEW CITATIONS ----------
NONE